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REVIEW ARTICLE

Why are ototopical aminoglycosides still first-line therapy for chronic suppurative otitis media? A systematic review and discussion of aminoglycosides versus quinolones

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Abstract

Objective: This systematic review aimed to establish that quinolones are as effective as aminoglycosides when used to treat chronic suppurative otitis media.

Method: The review included good quality, randomised, controlled trials on human subjects, published in English, that compared topical aminoglycosides with topical quinolones for the treatment of chronic suppurative otitis media.

Results: Nine trials met the criteria. Two studies showed a higher clinical cure rate in the quinolone group (93 per cent *vs* 71 per cent, $p = 0.04$, and 76 per cent *vs* 52 per cent, $p = 0.009$). Four studies showed no statistically significant difference in clinical outcome. A significant difference in microbiological clearance in favour of quinolones was shown in two studies (88 per cent *vs* 30 per cent, $p < 0.001$, and 88 per cent *vs* 30 per cent, $p < 0.001$).

Conclusion: Topical quinolones do not carry the same risk of ototoxicity as aminoglycosides. Furthermore, they are equal or more effective in treating chronic suppurative otitis media and when used as prophylaxis post-myringotomy. Topical quinolones should be considered a first-line treatment for these patients.

Key words: Otology; Otorhinolaryngology; Otitis Media; Otitis Media, Suppurative; Otitis Media, Purulent; Tympanostomy; Grommet Insertion; Quinolones; Aminoglycosides; Ciprofloxacin; Gentamicin; Neomycin; Framycetin; Tobramycin; Ofloxacin; Levofloxacin

Introduction

In the UK, aminoglycosides are considered as a first-line therapy for chronic suppurative otitis media (CSOM) patients with or without tympanostomy tubes.[1] Chronic suppurative otitis media has an estimated global incidence of 0.47 per cent, and in the UK approximately 1.5 per cent of adults are estimated to have active CSOM.[2,3] Serious complications occur if the infection is not effectively controlled, including hearing loss, intracranial spread of infection and venous sinus thrombosis.[4,5] Topical antimicrobial therapy is the mainstay of treatment for CSOM; Cochrane reviews have shown that topical antibiotics clear discharge better than antiseptics or placebo, and no benefit is derived from systemic antibiotics.[6,7]

Ototopical aminoglycosides are also administered following tympanostomy tube placement. In the UK, approximately 30 000 patients undergo this procedure annually, and a significant proportion of these receive a statutory dose of aminoglycoside (in ear drops) during the procedure.[8] A Cochrane review found that topical antibiotics are effective in reducing post-tympanostomy otorrhoea, but it is unclear which agent should be used.[9] The Scottish Intercollegiate Guidelines Network recommend a single dose of topical antibiotic at the time of tympanostomy tube insertion; post-operatively, they advocate using the same antibiotic used to treat the infected ear, but do not comment on the merits of specific antimicrobials.[10]

Ototopical aminoglycosides

The ototoxic effects of systemic aminoglycosides are well documented and accepted, and these effects are also seen following ototopical aminoglycoside administration.[11] Aminoglycosides applied to the middle ear diffuse across the round window membrane and can

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significantly concentrate in the inner ear.[12] A large amount of animal data are available showing ototoxicity from aminoglycosides applied directly to the middle ear.[13] Retrospective studies in humans have shown ototoxicity (mainly vestibular) resulting from topical gentamicin, and there are many published cases of cochlear and vestibular toxicity secondary to topical neomycin.[14–16] Concurrent use of many common medications (such as loop diuretics) may also augment the ototoxicity of aminoglycosides.

There are medicolegal implications in prescribing an ototoxic medication for use in the middle ear. Matthew *et al*. reviewed 15 years of clinical negligence claims in otology, through the National Health Service Litigation Authority, and found that 3.1 per cent of claims leading to damages were for ototoxicity following topical aminoglycoside treatment.[17] The Medical Protection Society advise caution in prescribing aminoglycosides in the presence of a grommet or perforation; they published a case of a patient suffering hearing loss following ototopical aminoglycoside, which was settled out of court.[18]

Ototopical quinolones

Topical quinolones have been used to treat ear infections since the 1980s and have minimal adverse effects.[19] A Cochrane review has shown that topical quinolones are effective at treating CSOM.[6] Trials have also shown quinolones to be effective in cases of otorrhoea with tympanostomy tubes.[20,21]

Unlike aminoglycosides, intratympanic ciprofloxacin does not cross the round window and is not found in the inner ear following application.[12] Macfadyen *et al*. did not report any ototoxicity in any of the trials reviewed.[6] Animal studies showed no change in hearing after ciprofloxacin was administered directly to the middle ear.[22–25] A systematic review concluded that ototopical ciprofloxacin was safe when used in the presence of a non-intact tympanic membrane in adults and children.[26] An Ovid and Pubmed database search using the keywords 'safety', 'toxicity', 'topical quinolones' and 'topical ciprofloxacin' did not reveal any articles that showed ototoxicity or other significant side effects following ototopical quinolone use.

Plasma levels of ciprofloxacin are not measurable after the administration of ototopical quinolones in patients with or without an intact tympanic membrane.[27–29]

Antimicrobial resistance

Concerns are frequently raised of increasing bacterial (particularly *Pseudomonas aeruginosa*) resistance to quinolones if they are more commonly prescribed. Whilst ciprofloxacin-resistant pseudomonas is increasingly isolated, there is no convincing evidence that ototopical quinolones cause this.[30] Resistance is more likely to be due to systemic therapy, with the highest rates of quinolone resistance isolated in urine samples and sputum samples from patients with cystic fibrosis.[31] Antibiotic resistance is commonly determined above a minimum inhibitory concentration; however, these values are of limited usefulness in guiding topical therapy, as concentrations many times higher are achieved compared to systemic therapy.[30] This may explain why reported antimicrobial resistance and clinical success are often mismatched in studies utilising topical therapy. No studies have shown that ototopical ciprofloxacin is systemically absorbed.[30]

National and international guidelines

In 2004, the American Academy of Otolaryngology – Head and Neck Surgery published a consensus panel review advising that quinolones be considered as a first-line treatment in the presence of a tympanic membrane perforation or ventilation tube.[32] In 2005, a Canadian guideline stated that 'gentamicin containing ear drops should not be used in patients with a non-intact ear drum'.[33] This was followed, in 2007, by similar position papers from the Australian and the New Zealand societies of otolaryngology head and neck surgery.[34,35] The New Zealand guidance stipulates that if potentially ototoxic drops are used then the patient should be informed of the risk of ototoxicity, which is between 1:1000 and 1:10 000.[35]

In 2007, ENT-UK issued a consensus statement which urged caution in using topical aminoglycosides in the presence of a perforated tympanic membrane.[1] However, ENT-UK stated that they could not recommend the use of quinolones as they are currently unlicensed in the UK. Of the 39 consultant otologists who formed the consensus panel, only 36 per cent supported the statement 'unlicensed topical quinolones should be used instead of aminoglycosides'.[1]

Aims

This study aimed to review trials comparing the use of topical quinolones and aminoglycosides in patients with a non-intact tympanic membrane. The primary aim was to establish whether there is evidence of superiority in treating otorrhoea. The trials were also examined for reported antibiotic resistance, side effects or significant events following administration.

Materials and methods

Inclusion criteria

The review included randomised, controlled trials on human subjects, published in English, that compared topical aminoglycosides with topical quinolones for the treatment of CSOM or for post-tympanostomy prophylaxis.

Method

The review was conducted and reported with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') statement.[36]

A search of the PubMed, Ovid (including the Allied and Complementary Medicine Database, the

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Cumulative Index of Nursing and Allied Health Literature, Embase, and Medline) and Cochrane databases was carried out. Bibliographies of review articles were examined. The search terms used were 'chronic suppurative otitis media', 'chronic otitis media', 'chronic discharging ear', 'grommets', 'ventilation tubes' and 'tympanostomy tubes', together with 'aminoglycosides', 'quinolones', 'fluoroquinolones', 'gentamicin', 'neomycin', 'framycetin', 'tobramycin', 'ciprofloxacin', 'ofloxacin' and 'levofloxacin'.

Duplicate articles were screened out from the list of results, which were then screened by title and abstract. During the next stage, full papers were reviewed; the articles were excluded if they did not meet the inclusion criteria or if they were of poor quality (aided by the Consolidated Standards of Reporting Trials 'CONSORT' checklist).

The search was up to date as of January 2015.

Results

The initial search identified 1351 articles. Eighty-one full text papers were examined. Nine trials of sufficient quality, which included 1116 patients, were found to meet the inclusion criteria.[37–45]

Study characteristics

The trials included were published over a 13-year period, from 1995 to 2008. They varied widely, making meta-analysis impossible.

The population and setting varied extensively across the studies. Seven trials focused on CSOM[37–43] and two investigated post-tympanostomy prophylaxis.[44,45] Two studies were community-based, examining a paediatric age group (ages 1–14 and 1–16 years) and included only Aborigines in Australia.[38,39] The trials investigating post-tympanostomy prophylaxis were carried out in the USA, in large ENT departments, and included only paediatric patients (aged 7–132 and 5–146 months).[44,45] The remaining trials were carried out in a variety of areas: Spain,[41] Hong Kong,[40] Jordan,[42] Turkey[43] and Israel.[37] Patients in these trials were treated in a hospital ENT setting and included a wider age range (14–71, 9–62, 9–65 and 19–73 years).

Follow up was limited in most of the studies. Three of the CSOM trials followed patients up to the end of the treatment course of 10 days;[41–43] the other studies followed patients up for 21, 30, 84 and 90 days.[37–40] The post-tympanostomy prophylaxis trials followed patients up for 10–14 and 21 days.[44,45]

Of the CSOM trials, six included ciprofloxacin,[37–39,41–43] one included ofloxacin,[40] two included gentamicin,[42,43] two included Sofradex® (dexamethasone, framycetin and gramicidin),[38,39] two included Otosporin® (hydrocortisone, neomycin and polymyxin)[40,41] and one included tobramycin.[37] The post-tympanostomy trials compared Cortisporin® (neomycin, polymyxin and hydrocortisone) with ciprofloxacin or ofloxacin respectively.[44,45]

The definition of CSOM was comparable through all the studies (defined as chronically discharging ears with a non-intact tympanic membrane).

Study bias

Of the CSOM trials, four were double-blinded[37–40] and three were not blinded.[41–43] Of the non-blinded trials, one was using different packaging and dosing schedules so abandoned blinding,[41] but the remaining two gave no explanation.[42,43] Of the two post-tympanostomy prophylaxis trials, both were double-blinded at the time of otoscopy.[44,45]

All studies were described as randomised; however, only three included adequate information on how randomisation was conducted.[38,39,45]

Although the study by Miro did match numbers of patients who had tympanostomy tubes or had undergone middle-ear surgery between the two treatment groups, the author did not comment on any difference in outcome between these patients and those who had not undergone these interventions.[41]

Fradis *et al*. randomised patients' ears separately if bilateral disease was present;[37] all other studies randomised each patient to one treatment. In all studies, the patients included had all undergone some treatment previously, but a treatment-free period prior to entering the study was standard (range, 3–14 days). In the study by Leach *et al*., all patients had previously received treatment with aminoglycosides, which had failed; this may have made it more likely that ciprofloxacin would be more effective.[38]

Otorrhoea resolution

Two studies showed a significantly higher clinical cure rate with quinolones compared to aminoglycosides.[39,40] A double-blind, randomised, single-centre trial by Tong *et al*. revealed that significantly more patients treated with ofloxacin had resolution of otorrhoea compared to those treated with Otosporin (93 per cent *vs* 71 per cent, $p = 0.04$).[40] Couzos *et al*. conducted a larger trial (111 patients completed treatment), which again was double-blind and randomised.[39] This multicentre trial compared ciprofloxacin with Sofradex in a paediatric aboriginal population and found a cure rate of 76.4 versus 51.8 per cent respectively ($p = 0.009$, absolute difference of 24.6 per cent, 95 per cent confidence interval (CI) = 15.8–33.4 per cent). They also recorded rates of perforation healing, but found no difference between the groups.[39]

Miro and the Spanish ENT Study Group conducted the largest study in this series.[41] They compared ciprofloxacin and Otosporin in a multicentre trial. They initially recruited 328 patients, but finished with 232. This was a well-constructed trial, with good information on power calculations and randomisation protocols. However, the trial was not blinded because of differences in the application of the drug (single *vs* multiple dose bottles and different dosing schedules). The study was designed and powered to prove the equivalence of

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ciprofloxacin to Otosporin in treating CSOM. They showed a resolution in otorrhoea of 91 per cent in the quinolone group and 87 per cent in the aminoglycoside group (absolute difference of 4 per cent, 90 per cent CI = 4.8–8.86 per cent), and concluded that ciprofloxacin was at least as effective as Otosporin in their population.

Leach *et al*. conducted their study in another paediatric aboriginal population.[38] This randomised, double-blind, single-centre trial compared ciprofloxacin and Sofradex in a group of 97 children who had persistent otorrhoea despite treatment with topical aminoglycosides. The findings showed resolution of otorrhoea in 70 per cent of the quinolone group and in 72 per cent of the aminoglycoside group (absolute difference of 2 per cent, 95 per cent CI = −20–16 per cent). The authors concluded that there was no clinical difference between the two treatments in the study population.[38]

A further two studies showed a statistically significant difference in microbiological cure in favour of quinolones over aminoglycosides (87.5 per cent *vs* 30 per cent, $p < 0.001$, and 88 per cent *vs* 30 per cent, $p < 0.001$).[42,43] These studies were unblinded and neither published specific data on clinical outcomes.

The study by Fradis *et al*., which randomised 60 ears to ciprofloxacin, tobramycin and placebo groups, was inadequately powered and therefore did not produce any statistically significant results.[37]

Post-tympanostomy primary outcomes

Both post-tympanostomy prophylaxis studies failed to show a statistically significant difference between the quinolones and aminoglycosides in reducing otorrhoea. In the study by Poetker *et al*., a control group which received no antibiotic prophylaxis was included, and a significant difference was seen between this group and both antibiotic groups (85.1 per cent clear in the control group *vs* 94.5 per cent in the Cortisporin group ($p = 0.01$) and 91.9 per cent in the ofloxacin group ($p = 0.04$)).[45] Poetker *et al*. also showed a significant improvement in blocked tube rates between the control group and antibiotic groups, but there was no significant difference between the quinolone and aminoglycoside groups.[45]

Secondary outcomes

All studies published details on bacteriology. *P aeruginosa* was cultured in all trials and was the most common in four of the six relevant studies.[38,39,42,43] Staphylococcus aureus was also cultured in all studies and was the most common in two of them.[40,41] Streptococci and enterococci were also documented, but were much less common.

Four papers provide details on antibacterial sensitivities; globally, there was more resistance to aminoglycosides than quinolones. The study by Miro described the highest resistance to quinolones, with 16 per cent reported resistance to ciprofloxacin; aminoglycoside resistance was higher, however, with 22 per cent of cultures resistant to neomycin.[41] In a study by Nawasreh and Fraihat, 52.3 per cent of pre-treatment bacteria were resistant to gentamicin, but none were resistant to ciprofloxacin.[42] Resistance to gentamycin developed in a further 29 per cent of patients post-treatment, whereas ciprofloxacin resistance remained at 0 per cent. Similarly, Tutkun *et al*. showed 0 per cent pre- and post-treatment resistance to ciprofloxacin, compared to 60 per cent pre-treatment and 70 per cent post-treatment resistance to gentamicin.[43] Leach *et al*. alone reported a small increase in ciprofloxacin-resistant pathogens after treatment, from 0 to 2 per cent.[38]

With regard to safety, across all the studies, only one patient was reported as having a significant change in pure tone audiometry values.[41] The patient was documented as having a new all frequency hearing loss after receiving aminoglycosides, but the study does not give any more details. No other significant side effects were recorded in any study. However, minor short-term side effects, including pruritus, vertigo and bitter taste, were recorded in several studies in both treatment arms.[39–41]

Discussion

This systematic review revealed nine good quality trials. There was no evidence that aminoglycosides were superior to quinolones in treating CSOM. Quinolones were effective at resolving otorrhoea and in accomplishing microbiological eradication. Quinolones were also as effective as aminoglycosides in reducing otorrhoea and tube blockage in patients with tympanostomy tubes.

The main limitation of the evidence base was a wide variation in population and location. No trials have been carried out in the UK. It is therefore unclear whether the outcomes would be comparable in a British population, which may have different bacteriology and patient factors. The numbers included in the trials are also relatively small (the largest comprised 232 patients) and contain possible sources of bias as discussed above.

Since the most recent relevant Cochrane review, in 2005,[6] there have been two new trials.[38,45] More importantly, that review excluded preparations without steroids. The question asked in this paper is more clinically relevant, as it seeks to inform the choice made by clinicians when choosing a medication for a patient with a non-intact tympanic membrane. In UK practice, aminoglycoside-steroid combinations are commonplace, whereas quinolones are rarely available in a combination form. This review included four trials that examined aminoglycosides combined with steroids; these were not commented on in the Cochrane review. The current review has shown that quinolones without steroids are equal to or better than aminoglycosides with steroids. The extra benefit to be gained from combining a steroid with a quinolone needs further research.

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The ENT-UK consensus document did not explore the efficacy of topical quinolones as they are not licensed.[1] Concern about increasing the prevalence of ciprofloxacin-resistant bacteria is cited in the ENT-UK document as another barrier. However, there is no convincing evidence of this. In the studies reviewed here, resistance to ciprofloxacin was low and there were no significant changes after treatment; conversely, there were high levels of aminoglycoside resistance, and this increased following exposure. Furthermore, the high levels of resistance reported in some texts do not compare to the efficacy of quinolones in treated CSOM; this may suggest that the resistance is partial and can be overcome by the high concentrations achieved topically.[3,46]

The General Medical Council (GMC) advises consulting the British National Formulary for guidance in prescribing medication. However, the British National Formulary is unclear in regard to prescribing therapy for CSOM. The British National Formulary states that ototopical aminoglycosides are contraindicated in the presence of a tympanic membrane perforation but that they are used by specialists.[47] It describes quinolone ear drops as 'an unlicensed but effective alternative'.

The GMC states that drugs should usually be prescribed within the terms of their licence.[48] However, the prescription of unlicensed medications is advised if 'there is no suitably licensed medicine that will meet the patient's need'.[48] An application for licensing of medication is not driven by clinical need but by market forces; a manufacturer needs a licence to import and market a drug.[49] Therefore, if there is not sufficient demand (and therefore profit) for a drug, then a company will not wish to market the drug and no licence will be applied for.

A search of non-UK national formularies revealed licences for topical quinolones for use with a non-intact tympanic membrane. In Australia, ear drops containing quinolones are licensed specifically for treating CSOM in adults and children.[50,51] Ciprodex® (ciprofloxacin-dexamethasone) is licensed in Canada for patients aged six years or older with non-intact tympanic membranes, and in the USA ciprofloxacin is licensed for ototopical use in three formations (Cipro® HC, Ciprodex and Cetraxal®).[52,53]

Conclusion

None of the available evidence from randomised trials has shown that aminoglycosides are superior to quinolones in treating CSOM. Topical quinolones do not carry the risk of ototoxicity that aminoglycosides do. Furthermore, they are equal or more effective in treating CSOM, or when used as prophylaxis post-myringotomy. They should therefore be considered as a first-line treatment for these patients, as is already the case in many countries around the world. If licensing is truly a barrier to the adoption of this policy, perhaps it is time that the UK's ENT community began to take a more proactive approach in calling for quinolones to be licensed for ototopical use.

References

1 Philips JS, Yung MW, Burton MJ, Swan IR. Evidence review and ENT-UK consensus report for the use of aminoglycoside-containing ear drops in the presence of an open middle ear. *Clin Otolaryngol* 2007;**32**:330–6
2 Monasta L, Ronfani L, Marchetti F, Montico M, Brumatti LV, Bavcar A *et al*. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS ONE* 2012;**7**:1–12
3 Ghosh S, Panarese A, Parker AJ, Bull PD. Quinolone ear drops for chronic otitis media. *BMJ* 2000;**321**:126–7
4 Yorgancılar E, Yıldırım M, Gun R, Bakır S, Tekın R, Gocmez C *et al*. Complications of chronic suppurative otitis media: a retrospective review. *Eur Arch Otorhinolaryngol* 2013;**270**:69–76
5 Dubey SP, Larawin V, Molumi CP. Intracranial spread of chronic middle ear suppuration. *Am J Otol* 2010;**31**:73–7
6 Macfadyen CA, Acuin JM, Gamble CL. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. *Cochrane Database Syst Rev* 2005;(4):CD004618
7 Macfadyen CA, Acuin JM, Gamble CL. Systematic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. *Cochrane Database Syst Rev* 2006;(1):CD005608
8 Sood S, Waddell AJ. Accurate consent for insertion and later removal of grommets. *J Laryngol Otol* 2007;**121**:338–40
9 Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. *Cochrane Database Syst Rev* 2013;(4):CD008512
10 Scottish Intercollegiate Guidelines Network. *Antibiotic Prophylaxis in Surgery* (SIGN Guideline no. 104). Edinburgh: SIGN, 2008
11 Helal A. Aminoglycoside ear drops and ototoxicity. *CMAJ* 1997;**156**:1056–8
12 Becvarovski Z, Bojrab DI, Michaelides EM, Kartush JM, Zappia JJ, LaRouere MJ. Round window gentamicin absorption: an in vivo human model. *Laryngoscope* 2002;**112**:1610–13
13 Roland PS, Rybak L, Hannley M, Matz G, Stewart MG, Manolidis S *et al*. Animal ototoxicity of topical antibiotics and the relevance to clinical treatment of human subjects. *Otolaryngol Head Neck Surg* 2004;**130**:S57–78
14 Bath AP, Walsh RM, Bance ML, Rutka JA. Ototoxicity of topical gentamicin preparations. *Laryngoscope* 1999;**109**:1088–93
15 Marais J, Rutka JA. Ototoxicity and topical eardrops. *Clin Otolaryngol Allied Sci* 1998;**23**:360–7
16 Matz G, Rybak L, Roland PS, Hannley M, Friedman R, Manolidis S *et al*. Ototoxicity of ototopical antibiotic drops in humans. *Otolaryngol Head Neck Surg* 2004;**130**:S79–82
17 Matthew R, Asimacopoulos E, Valentine V. Toward safer practice in otology: a report on 15 years of clinical negligence claims. *Laryngoscope* 2011;**121**:2214–19
18 Medical Protection Society. Problems with eardrops. Casebook 2008. In: http://www.medicalprotection.org/uk/resources/case-reports/case-reports/uk-problems-with-eardrops [20 August 2015]
19 Wai TK, Tong MC. A benefit-risk assessment of ofloxacin otic solution in ear infection. *Drug Saf* 2003;**26**:405–20
20 Heslop A, Lildholdt T, Gammelgaard N, Ovesen T. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhoea in children: the results of a randomized clinical trial. *Laryngoscope* 2010;**120**:2516–20
21 Dohar J, Giles W, Roland P, Bikhazi N, Carroll S, Moe R *et al*. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhoea through tympanostomy tubes. *Pediatrics* 2006;**118**:e561–9
22 Gates GA. Safety of ofloxacin otic and other ototopical treatments in animal models and in humans. *Pediatr Infect Dis J* 2001;**20**:104–7
23 Lemke L, McGee D, Prieskorn D, Wall M, Dolan D, Altschuler R *et al*. Safety of ciprofloxacin and dexamethasone in the guinea pig middle ear. *Arch Otolaryngol Head Neck Surg* 2009;**135**:575–80

https://doi.org/10.1017/S0022215115002509 Published online by Cambridge University Press

24 Kavanagh K, Parham K, Schoem S. Auditory function after a prolonged course of ciprofloxacin-dexamethasone otic suspension in a murine model. *Arch Otolaryngol Head Neck Surg* 2009;**135**:238–41
25 Daniel SJ, Munguia R. Ototoxicity of topical ciprofloxacin/dexamethasone otic suspension in a chinchilla animal model. *Otolaryngol Head Neck Surg* 2008;**139**:840–5
26 Wall G, Stroman D, Roland P, Dohar J. Ciprofloxacin 0.3 per cent/dexamethasone 0.1 per cent sterile otic suspension for the topical treatment of ear infections: a review of the literature. *Pediatr Infect Dis J* 2009;**28**:141–4
27 Clarós P, Sabater F, Clarós A Jr, Clarós A. Determination of plasma ciprofloxacin levels in children treated with topical ciprofloxacin 0.2% for tympanic perforation [in Spanish]. *Acta Otorrinolaringol Esp* 2000;**51**:97–9
28 García-Monge E, Sabater F. Study to determine plasma levels of ciprofloxacin after the administration of ciprofloxacin 0.3% ear drops in children with diffuse otitis externa [in Spanish]. *Pediatria Rural Y Extrahospitalaria* 1997;**27**:3–8
29 Force RW, Hart MC, Plummer SA, Powell DA, Nahata MC. Topical ciprofloxacin for otorrhoea after tympanostomy tube placement. *Arch Otolaryngol Head Neck Surg* 1995;**121**:880–4
30 Weber PC, Roland PS, Hannley M, Friedman R, Manolidis S, Matz G *et al*. The development of antibiotic resistant organisms with the use of ototopical medications. *Otolaryngol Head Neck Surg* 2004;**130**:S89–94
31 Blondeau JM, Suter ME, Borsos S, Misfeldt C. Canadian Pseudomonas aeruginosa susceptibility study from 48 medical centers: focus on ciprofloxacin. *Int J Antimicrob Agents* 1998;**10**:297–302
32 Roland PS, Stewart MG, Hannley M, Friedman R, Manolidis S, Matz G *et al*. Consensus panel on role of potentially ototoxic antibiotics for topical middle ear use: introduction, methodology, and recommendations. *Otolaryngol Head Neck Surg* 2004;**130**(3 suppl):S51–6
33 Rosser W, Pennie R, Pilla N, Anti-infective Review Panel. *Anti-infective Guidelines for Community-Acquired Infections*. Toronto: MUMS Guideline Clearinghouse, 2005
34 Black RJ, Cousins VC, Chapman P, Becvarovski Z, Coates HL, O'Leary SJ. Ototoxic ear drops with grommet and tympanic membrane perforations: a position statement. *Med J Aust* 2007;**186**:605–6
35 Gilbert JG, Dawes PJ, Mahadevan M, Baber WJ, Hall F. Use of ototoxic eardrops: a position statement from the New Zealand Society of Otolaryngology Head and Neck Surgery. *N Z Med J* 2007;**120**:U2646
36 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535
37 Fradis M, Brodsky A, Ben-David J, Srugo I, Larboni J, Podoshin L. Chronic otitis media treated topically with ciprofloxacin or tobramycin. *Arch Otolaryngol Head Neck Surg* 1997;**123**:1057–60
38 Leach A, Wood Y, Gadil E, Stubbs E, Morris P. Topical ciprofloxacin versus topical framycetin-gramicidin-dexamethasone in Australian aboriginal children with recently treated chronic suppurative otitis media. *Pediatr Infect Dis J* 2008;**27**:692–8
39 Couzos S, Lea T, Mueller R, Murray R, Culbong M. Effectiveness of ototopical antibiotics for chronic suppurative otitis media in Aboriginal children: a community-based, multicentre, double blind randomised controlled trial. *Med J Aust* 2003;**179**:185–90
40 Tong MC, Woo JK, Hasselt CA. A double blind comparative study of ofloxacin otic drops versus neomycin-polymyxin B-hydrocortisone otic drops in the medical treatment of chronic suppurative otitis media. *J Laryngol Otol* 1996;**110**:309–14
41 Miro N. Controlled multicentre study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymyxin B, neomycin, and hydrocortisone suspension. *Otolaryngol Head Neck Surg* 2000;**123**:617–23
42 Nawasreh O, Fraihat A. Topical ciprofloxacin versus topical gentamicin for chronic otitis media. *East Mediterr Health J* 2001;**7**:26–30
43 Tutkun A, Ozagar A, Koc A, Batman C, Uneri C, Sehitglu MA. Treatment of chronic ear disease. Topical ciprofloxacin vs topical gentamicin. *Arch Otolaryngol Head Neck Surg* 1995;**121**:1414–16
44 Morpeth JF, Bent JP, Watson T. A comparison of cortisporin and ciprofloxacin otic drops as prophylaxis against post-tympanostomy otorrhoea. *Int J Pediatr Otorhinolaryngol* 2001;**61**:99–104
45 Poetker DM, Lindstrom DR, Patel NJ, Conley SF, Planary VA, Link TR *et al*. Ofloxacin otic drops vs neomycin-polymixin B otic drops as prophylaxis against early postoperative tympanostomy tube otorrhea. *Arch Otolaryngol Head Neck Surg* 2006;**132**:1294–8
46 Poole MD. Bacterial resistance to quinolone otic drops is nearly zero. *Ear Nose Throat J* 2007;**86**:13–14
47 Joint Formulary Committee. *British National Formulary (BNF) 68*. London: BMJ/Pharmaceutical Press, 2014
48 General Medical Council. Prescribing guidance: Prescribing unlicensed medicines. In: http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp [20 August 2015]
49 Medicines and Healthcare Products Regulatory Agency. Apply for a licence to market a medicine in the UK. In: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/index.htm [20 August 2015]
50 Therapeutic Goods Administration. CILOQUIN® (ciprofloxacin) 0.3 per cent Ear Drops. Australia 2013. In: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02436-3 [20 August 2015]
51 Therapeutic Goods Administration. CILOXAN® (ciprofloxacin) 0.3 per cent Ear Drops. Australia 2014. In: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02301-3 [20 August 2015]
52 Alcon Canada. Product Monograph: Ciprodex. Health Canada 2004. In: http://webprod5.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng [31 August 2015]
53 US Food and Drug Administration. FDA approved drug products. Search: Ciprofloxacin. In: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [10 March 2015]

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